

FURTHER EXPERIMENTAL RESEARCHES ON THE ETIOLOGY OF ENDEMIC GOITRE*

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OBJECT OF THE RESEARCH

In a communication which I had the honour to make to the Royal Society, on the 26th November, 1908, I described the results of my experimental researches on the etiology of goitre up to that date, as follows:—

1. Goitre can be experimentally produced in man by the administration of the matter in suspension separated by filtration from waters which are known to be goitre-producing.

2. Goitre cannot be so produced when the suspended matter is boiled.

3. The disease is due, therefore, not to the mineral but to the living component of the suspended matter, in other words, to a living organism of disease.

4. The incubation period of experimentally produced goitre is thirteen to fifteen days.

5. Goitre can be cured by the administration of intestinal antiseptics. It is possible, therefore, that the organism which is the cause of the disease is parasitic in the human intestine.

These conclusions were based on the results of experimental observations carried out on man during the years 1907-1908. It has been the object of the present research to test their accuracy by

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experimentation on a larger number of men. My investigations may be summarised as follows:—

I. The experimental administration to man of suspended matter, separated by filtration and sedimentation from goitre-producing waters.

II. The experimental administration to man of suspended matter from the same source, which had been subjected to *boiling* for at least ten minutes.

III. The effect of the administration of filtered goitre-producing water to man under experimental conditions.

IV. The action exercised by the lactic ferments when applied to the treatment of goitre.

V. The effect on dogs of the administration of extracts from faeces of goitrous individuals.

I and II. THE EXPERIMENTAL ADMINISTRATION TO MAN OF THE (a) UNTREATED AND (b) BOILED SUSPENDED MATTER OF GOITRE-PRODUCING WATERS

Experiment G.—Carried out during October and November, 1909.

Thirteen healthy young men, aged between eighteen and twenty-four years, volunteered for this experiment. All were new-comers to the district, and were in every respect perfectly normal. During the whole course of the experiment the men lived under the strictest guard. Their diet was chiefly vegetable. They were kept at hard exercise, and were not permitted to handle the soil, or to drink or eat anything whatsoever except what was prescribed. The hygienic conditions of life under which they lived were excellent. They were encamped on a non-goitrous site, and were provided with water for drinking, bathing, and other domestic purposes, from the Bermis spring, which is non-goitre producing, but which, as an additional precaution, was boiled. In no case was the restraint imposed upon them broken through.

Kashrote Village water was used for the purposes of this experiment. Goitre prevails in this village to the extent of 45 per cent. The water flows through a narrow irrigation channel, which receives the drainings from cultivated land, and is subjected to much contamination both from human and animal sources. This

water, which at the time of collection was purposely made muddy by agitation, was brought daily from the village to the camp on the hilly ground above, a distance of about one and a half miles. It was allowed to stand in suitable vessels and to deposit its sediment. Four ounces of this sediment were administered to each subject before the morning and evening meals for thirty days.

The results were as follows:—

1. Nine individuals showed no change in the thyroid gland which could be detected by physical examination.

2. In two other cases a uniform swelling of the organ was observed on the tenth day of the experiment. The swelling gave rise to feelings of discomfort, and complaint was made of throbbing in the neck and the tightness of collar bands which had previously fitted well. The measurement of the neck increased by one centimetre in one case, by one and a half in the other. The enlargement persisted up to the twentieth day of observation and then gradually disappeared; the gland was observed to have regained its normal size on the thirtieth day, when the experiment was concluded.

3. In the two remaining cases a more marked reaction on the part of the thyroid gland was observed. In both these cases the right lobe was chiefly affected, and the swelling was accompanied with feelings of discomfort, throbbing in the neck and tightness of the neck band. The measurement of the neck increased one and a half centimetres in one case, and slightly over one centimetre in the other. The enlargement made its appearance between the tenth and fifteenth days of the experiment in each of these cases, and persisted up to the thirtieth day, when the experiment was terminated.

Unfortunately, no photographic records of these cases could be obtained owing to the fact that I had just returned from Europe, and my materials for obtaining such records had not reached me. The thyroid enlargements observed in the two latter cases resembled very closely that shown in Figs. 2 and 9.

EXPERIMENT H.—Carried out during October and November, 1909.

The conditions of this experiment were precisely similar to those detailed in the previous one. In this case, however, the thirteen individuals who volunteered for it were given the same

Kashrote water sediment *which had been previously boiled for ten minutes*. In none of these individuals could any reaction on the part of the thyroid gland be detected. The experiment, which lasted thirty days, was carried out concurrently with Experiment G, and formed a very suitable control to it.

EXPERIMENT I.—Carried out from 15th March to 9th May, 1910.

The conditions of this experiment were precisely similar to those of G and H, with the exception that in this case the goitre-producing water of Kashrote was filtered through a Berkefeld house-filter. The deposit on the candle was washed off in distilled water, and a quantity of this dark grey mixture, equal to about two ounces, was given to each subject in milk before the morning and evening meals. Ten individuals volunteered for this experiment. Their average age was twenty-two. All were enjoying excellent health and were in every respect normal.

Of these individuals four showed no reaction whatever on the part of the thyroid gland during the fifty-five days the experiment lasted. One developed a slight degree of enteritis on the fifteenth day when the experiment in his case was discontinued. The following is the more detailed account of the alterations observed in the remaining five cases:—

1. G.M.—15.3.—The thyroid gland was normal. The measurement of the neck on this date, when the experiment commenced, was thirty-three and a half centimetres. The subject was photographed. (Fig. 1)
- 31.3.—The measurement of the neck was thirty-four and a half centimetres. The right lobe of the thyroid gland was slightly enlarged. There was distinct fullness of the neck on that side. During the act of deglutition the right lobe of the organ was felt to pass under the fingers as a rounded boss. The subject complained of tightness of the shirt collar and of throbbing in the neck.
- 6.4.—There was no marked change to be recorded. The subject complained of the same symptoms as at the previous examination. The outline of the gland was readily seen and felt. The measurement of the neck was thirty-four centimetres.
- 10.4.—There was no appreciable change on physical examination. The measurement of the neck was thirty-four and a half centimetres. The subject complained of inability to button his collar band.
- 15.4.—The thyroid gland was noticeably enlarged. The enlargement was especially well seen during the act of swallowing. The measurement of the neck was thirty-five centimetres. The subject was photographed. (Fig. 2.)

- 21.4.—The measurement of the neck was thirty-four and a half centimetres.
- 1.5.—The thyroid enlargement was not so evident. The neck measured thirty-four centimetres.
- 9.5.—The thyroid gland was undoubtedly smaller on this date than on the 15th April. The measurement of the neck was thirty-four centimetres. The experiment was discontinued and the subject was given thymol, ten grains night and morning. No trace of enlargement of the thyroid gland was observable one month later.
2. S.A.—15.3.—The thyroid gland was normal. The measurement of the neck was thirty-three centimetres. The subject was photographed. (Fig. 3.)
- 31.3.—There was slight enlargement of the left lobe of the thyroid gland which was clearly seen and readily felt when the subject swallowed. The measurement of the neck was thirty-three and a half centimetres.
- 6.4.—The thyroid gland was noticeably enlarged especially on the left side. The enlargement was well seen on swallowing. The subject complained: "that the neck of his shirt had been very tight for the last five or six days; and that he could only button it by pulling the collar band up above the swelling; that he slept a great deal; that he was light-headed; that there was much throbbing in the neck." The measurement was thirty-four and a quarter centimetres.
- 10.4.—No appreciable change was observed since the date of the previous note. The neck measured thirty-four and a half centimetres.
- 15.4.—The thyroid gland showed well-marked enlargement over its whole extent, but especially of the left lobe. The neck measured thirty-five centimetres. The subject was photographed. (Fig. 4.) He had been quite unable to button the neck of his shirt, which previously fitted well, and had tied the button-holes together with cord. (Fig. 5.)
- 21.4.—The neck measured thirty-five centimetres. There was no change since date of previous note.
- 1.5.—The neck measured thirty-four and a half centimetres.
- 9.5.—The neck measured thirty-four and a quarter centimetres, but looked decidedly smaller than on the 15th April. The subject was noticed to be somewhat anaemic. The experiment was discontinued and the subject placed under treatment by thymol and tonics. No trace of enlargement could be detected one month later.
3. A.M.—15.3.—The thyroid gland was normal. The neck measured thirty-four centimetres. The subject was photographed. (Fig. 6.)
- 31.3.—There was considerable enlargement of the gland in the region of the isthmus, which could be felt as a rounded boss under the finger, and was noticeable on swallowing. The neck measured thirty-four and a half centimetres.
- 6.4.—The right side of the neck was fuller than at the previous examination. The swelling of the isthmus was more marked, and, on digital examination was found to be dumb-bell-shaped. The left side of the dumb-bell was larger than the right. The swelling of the isthmus was well seen on swallowing, but it partially disappeared behind the sternum when the subject was at rest. The subject complained of tightness of his collar and throbbing in the neck. Measurement showed the neck to be thirty-five centimetres in circumference.

- 15.4.—The neck measured thirty-five and a half centimetres and the swelling of the thyroid and especially of the isthmus was more noticeable than at the last examination.
- 21.4.—There was no change to be found on physical examination. The subject was photographed. (Fig. 7.)
- 31.4.—The neck measured thirty-four and a half centimetres, and the thyroid appeared to be slightly smaller.
- 9.5.—There was no noticeable alteration since the day of the last examination. The neck measured thirty-four and a half centimetres. The experiment was discontinued and the subject placed under treatment.
4. A.D.—15.3.—The thyroid gland was normal. The circumferential measurement of the neck was thirty-four centimetres. The subject was photographed. (Fig. 8.)
- 31.3.—The neck measured thirty-five centimetres. There was some fullness under the sterno-mastoids, and the whole outline of the gland was readily seen when the subject swallowed. The subject did not complain of any symptoms.
- 6.4.—The neck measured thirty-five and a half centimetres. There was no appreciable difference from the appearances observed at the date of the last note.
- 15.4.—The neck measured thirty-five and a half centimetres. The subject complained of no symptoms though the gland was seen to be undoubtedly, but slightly, enlarged. The subject was photographed. (Fig. 9.)
- 9.5.—The neck measured thirty-five and a half centimetres. There was no further change to be recorded. The experiment was discontinued and the subject placed on treatment by thymol. No trace of enlargement could be found fifteen days later.
5. F.A.—In this case the original measurement of the neck was thirty-two and a half centimetres. On the twentieth day of the experiment the subject complained of a sense of fullness in the neck and of tightness of his collar band. The neck then measured thirty-three and a half centimetres. There was some fullness under the sterno-mastoids, and the outline of the gland was well marked and easily palpable. No further enlargement occurred, and on the 15th April the gland was found to have returned to its normal size.

EXPERIMENT J.—Carried out from 15th March to 9th April, 1910.

The conditions of this experiment were in all respects similar to those of Experiment I, with the exception that the *boiled* residue was given instead of the untreated residue. Ten individuals, of whom the average age was twenty-two, volunteered for the experiment. Amongst these were five in whom the thyroid gland was larger than normal; it was considered that these subjects might respond more readily to goitrous influences than those in whom the gland was perfectly normal.

The duration of the experiment was fifty-five days. It was carried out concurrently with the preceding one. In no case could the slightest increase in size be detected by any method of examination. In the five cases, in whom the thyroid was normal at the commencement of the experiment, there was no alteration whatever. In the other five subjects, in whom at the commencement the gland was somewhat larger than normal, the original and final measurements were as follows:—

	Original Measurement.				Final Measurement.			
D. B.	34	33½	
T. R.	34	33	
D. R.	32	30½	
K.	35	34½	
R.	33½	33	

These results show that the tendency to alteration in size of the thyroid was, in these five individuals, in the direction of diminution and not of increase.

The results of the foregoing experiments may be summarized as follows:—

1. Of twenty-three individuals who consumed the suspended matter of goitre-producing waters, six showed an increase in size of the gland, which persisted in a more or less well-marked manner up to the end of the experiment. Three others showed a thyroid hypertrophy of a transitory character.

2. Of twenty-three individuals who consumed the *boiled* suspended matter of goitre-producing waters none showed the slightest tendency to an increase in size of the thyroid gland.

These results are to be contrasted with those of my former series, which were:—

1. That of thirteen individuals who consumed the untreated residue of the goitre-producing waters of Kashrote, four developed a noticeable swelling of the thyroid gland, while two others showed an increase in size of the organ demonstrable by measurement and evident to the touch.

2. That of eight individuals who consumed the *boiled* residue of the goitre-producing waters of Kashrote, none developed any swelling of the thyroid gland, and this although three were individuals peculiarly likely to respond to goitrous influences.

The combined results of both series of experiments show :—

1. That of thirty-six individuals who consumed the untreated suspended matter of a notoriously goitre-producing water, ten developed a noticeable hypertrophy of the thyroid gland, while five showed a swelling of the organ of a transitory character.

2. That of thirty-one individuals who consumed the same suspended matter *which had been previously boiled*, none showed any reaction in the direction of increase in size of the thyroid gland.

The results of these experiments justify the following conclusions :—

1. There exists in suspension in the water of goitrous localities some unknown agent which is capable of initiating an hypertrophy of the thyroid gland.

2. This agent can be destroyed by boiling for ten minutes.

III. THE EFFECT OF THE ADMINISTRATION OF THE FILTERED GOITRE-PRODUCING WATERS TO MAN UNDER EXPERIMENTAL CONDITIONS

Having demonstrated that there exists in suspension in goitre-producing waters a substance which is capable of initiating an hypertrophy of the thyroid gland, and that this substance is readily destroyed by boiling, it became necessary to ascertain by carefully conducted experimental observations whether filtration deprived the water of its goitre-producing properties. For this purpose seven individuals were selected who consumed the filtrate of Kashrote water at the same time that the subjects of Experiment I were consuming the suspended matter separated from it by filtration. The same minute precautions were adopted in the case of these men as in those of Experiment I. In four of these the thyroid gland was perfectly normal on the 15th March, when the experiment commenced; the other three were the subjects of incipient goitre. All seven drank only the filtered Kashrote water for fifty-five days, with the following results:—The four normal individuals showed no change whatever, while the three men in whom the thyroid was enlarged showed a considerable reduction in size of this organ. This result indicates that the process of filtration renders water innocuous which was previously goitre-producing; the

suspended matter removed from the water by this process having actually produced a thyroid hypertrophy in five out of ten individuals who consumed it, while the subjects of the present experiment were consuming the filtrate. Water so purified not only does not cause a thyroid hypertrophy, but it exercises a curative influence on incipient cases of goitre.

The beneficial influence of filtration of goitre-producing waters is nowadays so well recognised, and has been demonstrated on such a large scale in the case of many public water supplies that it appears almost unnecessary to emphasize it. There are still, however, many scientific men who adhere to the chemical cause of goitre, and these are seeking in radio-active substances fresh support for their view. My experiments make it clear that, for the Hindu Kush region at least, where my researches have been carried out, the noxious principle of goitre is found only in suspension in the water and does not exist in solution; and, that if the cause of goitre is a chemical one it is of such a nature as to be unable to pass through pores of a Berkefeld filter and to be readily destroyed by boiling.

The hypertrophy of the thyroid gland, which is capable of being induced in the way described in the foregoing experiments, exhibits the following characteristics:—

1. It makes its appearance usually between the tenth and the fifteenth days of the experiment.
2. It shows a marked tendency to fluctuate in size.
3. It reaches its point of maximum size between the twenty-fifth and thirtieth days of the experiment.
4. It may completely disappear under the conditions of the experiment.
5. The hypertrophy of the gland is not great nor is it progressive under the conditions of the experiment. The tendency being towards a diminution in size from the thirtieth day onward.
6. It is accompanied, as a rule, with certain subjective symptoms of throbbing in the neck, feelings of fullness and discomfort.

The fluctuations of the thyroid gland observed in the individuals under the conditions of my experiments, exhibit a very striking resemblance to those of the endemic of goitre which are known to

occur in large communities. The endemic is subject to periods of increase and decrease. It shows a marked tendency to increase in an infected locality till a point of maximum intensity for that locality is reached, after which the disease tends to decline. This increase or decrease of the endemic in a given locality is rarely uniformly progressive but exhibits a marked periodicity.

NOTES ON SECONDARY FACTORS IN THE PRODUCTION OF GOITRE

In the report of my first series of experiments on man, carried out on the lines which I have here indicated, and which was published in full in the 'Quarterly Journal of Medicine' (April, 1909), I made the following comments with reference to artificially produced thyroid hypertrophy:—'The conditions of these experiments differed from those under which the inhabitants of Gilgit live in certain important respects. The men were not subjected to the debilitating influences of defective hygiene, vitiated atmosphere, imperfect dietary, endemic disease and the like. Nor did that potent source of infection among an agricultural community, namely, contamination of the hands and food by the soil of an infected locality come into operation in their case. It is to the absence of such influences as these that I attribute the fact that the experimentally produced goitres were neither large nor progressive. . . . I am convinced, therefore, that there are conditions provided by a residence in a goitrous locality apart from the water supply which are important determining factors in the production of the disease, and that in the absence of these secondary factors the organism, which is the real causal factor is of feeble pathogenicity.' My study of goitre during the past eight years has led me to attach great importance to the following factors as possessing a marked secondary influence on the development of thyroid hypertrophy in endemic localities:—

A. Factors directly influencing the thyroid gland which render it less able to counteract the action of the toxic agent of goitre without undergoing hypertrophy:—

- (a) Hereditary influences: Other things being equal, the children of goitrous women appear to be more likely to develop goitre than the children of normal women.

- (b) The marked influence of age, sex, puberty, menstruation, pregnancy, sexual activity on the functional activity of the thyroid gland: the added strain of goitrous influences at a time when the gland is already working at high pressure very markedly favours the development of a goitre.
- (c) The influence of unhygienic conditions of life: defective air space, on which the so-called 'epidemics' of the disease are largely dependent; improper food or defective food supply; damp soil; the 'causes multiples' of the older French writers.
- (d) The influences of certain infectious diseases on the thyroid gland such as rheumatism, rheumatoid arthritis, malaria, etc.
- (e) The influence of emotional states.

B. Factors which favour infection:—

- (a) The influence of occupation and habits of life, whereby individuals are rendered more liable to infection from the soil which is the natural habitat of the toxic agent of the disease.
- (b) The influence of temperature: goitre is more likely to develop in temperate climates or at temperate seasons of the year.
- (c) Susceptibility: new-comers to a district are very prone to contract the disease.

C. Factors favouring the action of the virus of the disease at the time of its entry into the body:—

- (a) An organically impure water.
- (b) Much mineral matter in suspension in the water.
- (c) Very hard waters, especially those containing much lime, magnesium, or iron in solution.

These factors, I believe, act by inducing abnormal states of the lining membrane of the gut, and thus favour the development or action of the toxic agent of goitre. To them subsequent experience may add others, but they are those which I have found to be of the chief importance in the regions where my researches have been carried out. These influences are, in short, those which observers

from the remotest times have considered to be primarily causal in the production of the disease. Their importance is undoubtedly great, but secondary only to the true causal factor which remains still to be discovered.

IV. THE ACTION EXERCISED BY THE LACTIC FERMENTS WHEN APPLIED TO THE TREATMENT OF GOITRE

I have previously drawn attention to the curative action of intestinal antiseptics, notably thymol and beta-naphthol, in cases of goitre, and I have regarded the action of these drugs as strong, though not conclusive evidence that the responsible agent in the production of the disease has its habitat in the intestinal tract of man. The action exercised by the lactic acid ferments when applied to the treatment of goitre affords additional evidence in favour of this view. In carrying out this line of treatment I have used the fresh cultures in milk of the *Bacillus bulgaricus*. I have treated up to the present time only eight cases in this way, but the results have been so striking that it is necessary to record them in this place. I have hitherto employed only milk as a medium for the administration of this bacillus but, owing to the scarcity of milk in this country, some other medium must in future be employed. Twelve to twenty ounces of 'soured milk' were given to each patient every morning before the first meal of the day for periods of one month to six weeks. The cases were all of several months standing, and during treatment there was no change whatever in the manner of life of the patients. They were treated as external cases, and carried out their work in the fields as usual. The results cannot be attributed, therefore, to change of locality, habits of life or water supply. Of these eight cases four were cured, two improved, and two showed no appreciable difference after six weeks. In those cases which were benefited by the treatment, it was observed that the thyroid gland began to show evidence of diminution in size about the tenth day of treatment, and, that the patients lost flesh. This latter fact is of considerable interest, as it is observed to occur also in the treatment of goitre by means of thymol, beta-naphthol and iodine. Figs 10, 11 and 12 represent various stages in the treatment of one of these cases. Fig. 11 shows the case after fifteen days, and Fig. 12 after thirty days of treatment.

V. THE EFFECT ON DOGS OF THE ADMINISTRATION OF EXTRACTS FROM THE FAECES OF GOITROUS INDIVIDUALS

EXPERIMENT K.—Carried out from the 10th December, 1909, to 8th March, 1910.

Nine healthy puppies were confined in a pen for a period of eighty-eight days and were fed during this time on watery extracts from the faeces of goitrous individuals. All due precautions were observed to prevent infection from other sources, such as the provision of a pure water supply, etc. Three control animals of a like age were confined in a neighbouring pen for the same length of time. The results were entirely negative. Post-mortem examination of the thyroid gland in these animals revealed no deviation from normal in the direction of hypertrophy. The thyroid gland of the nine puppies, to which extracts of the faeces were given, varied in weight from one-twelve-hundredth to one-twenty-four-hundredth part of the body weight. In the case of the control animals the weight of the thyroid varied from one-thousandth to one-fifteen-hundredth part of the body weight.

VI. RESULTS OF THE RESEARCH

1. There exists in suspension in waters which are known to be goitre-producing an agent which is capable of initiating an hypertrophy of the thyroid gland.

2. This agent is destroyed by boiling, and is removed from the water by filtration.

3. This agent is, therefore, either a living organism or a chemical substance the noxious properties of which are destroyed by heat.

4. The incubation period of experimentally produced goitre is usually about ten to fifteen days.

5. Goitre can be cured by the administration of intestinal antiseptics. The lactic ferments exercise a curative action when applied to the treatment of incipient goitres.

6. It is very probable that the agent which is responsible for the production of goitre is a living organism parasitic in the human intestine.

7. The disease cannot be communicated to dogs by means of watery extracts from the faeces of goitrous individuals.

These results confirm in detail those which I communicated to the Royal Society on 26th November, 1908.

EXPLANATION OF PLATES I AND II

- Fig. 1.—‘G.M.’ referred to in Experiment I. Shows appearance of neck at the time the experiment was commenced. Measurement, $33\frac{1}{2}$ centimetres.
- Fig. 2.—The same subject. Photograph taken on thirtieth day of the experiment. Measurement, 35 centimetres.
- Fig. 3.—‘S.A.’ referred to in Experiment I. Shows appearance of neck at the time the experiment was commenced. Measurement, 33 centimetres.
- Fig. 4.—The same subject. Photograph taken on the thirtieth day of the experiment. Measurement, 35 centimetres.
- Fig. 5.—The same subject. Photograph taken on the thirtieth day of the experiment. Shows subject’s method of fastening his shirt-band which buttoned comfortably prior to the commencement of the experiment.
- Fig. 6.—‘A.M.’ referred to in Experiment I. Shows appearance of the neck at the time the experiment was commenced. Measurement, 34 centimetres.
- Fig. 7.—The same subject on the thirty-sixth day of the experiment. Measurement, $35\frac{1}{2}$ centimetres. The enlargement of the isthmus and of the right lobe of the gland is well seen.
- Fig. 8.—‘A.D.’ referred to in Experiment I. Shows the appearance of the subject’s neck prior to the commencement of the experiment. Measurement, 34 centimetres.
- Fig. 9.—The same subject on the thirtieth day of the experiment. The increase in size is slight but evident. Measurement, $35\frac{1}{2}$ centimetres.
- Fig. 10.—Boy, aged twelve years, the subject of a goitre said to be of several months standing.
- Fig. 11.—The same case after fifteen days’ ‘soured milk’ treatment.
- Fig. 12.—The same case after thirty days’ ‘soured milk’ treatment.



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